TAVI- Is Stroke Risk the Achilles Heel of Percutaneous Aortic Valve Repair?

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What is the name of the only valve approved by the FDA for transcatheter aortic valve implantation?

1. The CoreValve
2. The Sapien Valve
3. The Mosaic Valve
4. The MagnaEase Valve
5. The Cribier Valve

What is the name of the trial that led to FDA approval of the Sapien Valve?

1. The PIVOTAL trial
2. The TAVI trial
3. The PARTNER trial
4. The COOL trial
5. The HEARTVALVE trial
Transcatheter Aortic-Valve Implantation (TAVI)

- Review of the historical perspective of TAVI
- Contemporary results: the PARTNER and the PIVOTAL trials
- What is the status on the risk for stroke?

Aortic Stenosis

- Most common valvular lesion in the US (2-7% calcifications in >65 yo)
- Etiology: degenerative, bicuspid, rheumatic
- Symptoms: angina, syncope, CHF
- Once symptoms occur, survival decreases (1 year: 50%; 2 years: 30%; 3 years: 20%)

- Indications for surgery
  - Symptoms with severe stenosis
  - AWA<1.0cm²
  - Gradients>40mmHg
  - Aortic jet velocity >4cm/s
  - Mod-severe stenosis, undergoing CABG or aortic surgery
  - Asymptomatic with:
    - LV systolic dysfunction
    - Abnormal response to exercise
    - Extremely severe AS (AWA <0.6cm², gradient>60mmHg)

Classical Treatment for Aortic Stenosis:
Aortic Valve Replacement

- Mechanical Valves
- Bioprosthetic Valves
  - Stented
  - Stentless
  - Aortic Homografts
  - Pulmonary Autografts
Patient Population for TAVI

Severe Aortic Stenosis

- Medical Management
- Refused Surgery
- Not Referred to Surgery
- Balloon Valvuloplasty
- High Risk Patients
- Surgical AVR

30% are not candidates for AVR:
- comorbidities
- age
- LV dysfunction

First Procedure

- 2000: Bonhoeffer et al. described the transvenous placement of a pulmonary-valve prosthesis and speculated that a similar technology might be used for other cardiac valves
  - Lancet, 2000

- 2002: Dr. Alain Cribier performed the first transcatheter insertion of an aortic-valve prosthesis.
  - Circulation, 2002

Transcatheter Aortic Valve Implantation (TAVI)

- Transcatheter aortic valves for severe AS

There is NO excision of valve leaflets, but a forceful spreading of the valve cusps against the wall and anchoring of the prosthesis without sutures.

Sapien (Edwards)

CoreValve (Medtronic)
TAVI Patient Candidates: “Inoperable” AS Patients (Cohort B)

- >50% chance of mortality or never leaving chronic care facility
- High “frailty” index
- Porcelain aorta by CT
- Chest wall irradiation
- Severe chest wall deformity
- End-stage COPD
- Cirrhosis
- Neurocognitive dysfunction

TAVI Patient Candidates: “High Risk” AS Patients (Cohort A)

- Pts currently undergoing AVR with high risk of operative mortality and morbidity
  - Elderly (>80 yo), renal failure, severe COPD, cerebrovascular disease, prior cardiac surgery, PVD, etc
- “Untreated” symptomatic severe AS patients
  - Patients refusing surgery
  - High risk surgical patients
  - Patients not referred to surgery
- STS Predicted Risk >10%, Logistic EuroSCORE >30%

Design Requirements

- Trileaflet biologic tissue valve
  - Good hemodynamic valve performance
  - No/minimal paravalvular leak
  - Valve durability
- Collapsible/Expandable circular stent platform
  - Avoid coronary artery obstruction
  - Landing zone annular/subannular without MV impingement
  - Stent durability and fatigue resistance
- Flexible delivery system
  - Adequate vascular access <22Fr
  - Hemodynamic stability during implantation

Hybrid Operating Room

  - Webb J, Cribier A Eur Heart J 2011;32:140-147
Retrograde Femoral Approach
- Good vascular access
- No arch pathology

Transapical Approach
- Poor vascular access
- Aortic arch pathology
- Difficult retrograde crossing

TAVI Numbers: Worldwide Prediction
Over 20,000 cases to date

Trends in Valve Prosthesis Selection
- Bioprosthetic: 41%
- Neo-Valve: 58%
- Mechanical: 11%
- Other: 9%
Transcatheter Aortic-Valve Implantation (TAVI)

- Review of the historical perspective of TAVI

- Contemporary results: the PARTNER and the PIVOTAL trials

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PARTNER- Cohort B (inoperable)

- 358 patients with AS considered “inoperable”
- 21 centers (17 in the US)
- 1 year outcomes
- Primary endpoint: death from any cause
- Coprimary endpoint: composite of the time to death from any cause or the time to first occurrence of repeat hospitalization due to valve-related or procedure-related clinical deterioration

PARTNER- Cohort B Primary Endpoints

Leon et al, NEJM 2010
### PARTNERS- Cohort B: 2 years

**Table 1. Clinical Outcomes at 30 Days and 1 Year**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
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<tbody>
<tr>
<td>TAXI (n=179)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from cardiovascular cause</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleeding with transfusion</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Major bleeding with reintervention</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Any bleeding with reintervention</td>
<td>0.03</td>
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**Symptoms Status**

**Figure 3. Symptoms Status Over Time**

- NYHA Class
- Patient Status

**PARTNERS- Cohort B: 2 years**

**Table 1. Clinical Outcomes at 1 and 2 Years in the Intention-to-Treat Population**

<table>
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<tr>
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<th>2 Years</th>
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Cohort B- Inoperable

- **Summary of findings**
  - Standard medical therapy (including balloon valvuloplasty) did not alter the natural history of AS
  - Transfemoral TAVI is superior to standard medical therapy (reducing death, NNT=5)
  - TAVI is associated with a significant reduction in symptoms
  - There are more neurological events, vascular complications and bleeding in TAVI.
  - Echo findings demonstrated an excellent performance of the valve at follow-up (even in the presence of mild paravalvular regurgitation)

PARTNER- Cohort A (high-risk)

- 699 high-risk patients with severe AS
- 25 centers
- AVR or TAVI
- Primary endpoint: death at 1 year
- Hypothesis: TAVI is not inferior to AVR

PARTNER – Cohort A: 1 year

Smith et al, NEJM 2011
PARTNER- Cohort A: 2 years

CoreValve Implantation Zone

Cohort A- High Risk

- Summary of findings
  - TAVI is NOT inferior to AVR in high risk patients with regards to survival
  - The profile of post-operative complications is different

  **TAVI:**
  - increased early risk of stroke
  - increased vascular complications

  **AVR:**
  - increased bleeding
  - increased atrial fibrillation

FDA approval of the Sapien valve for “inoperable” patients in November 2011.

Expected review for “high risk” patients in June 2012
CoreValve US Pivotal Trial Design

Extremely Risk Study
- Predicted 30d mortality >50%
- Primary endpoint all cause mortality + stroke
- Alternative arterial access possible

High Risk Study
- Predicted 30d mortality >15%
- 1:1 randomized to TAVI vs AVR
- Primary Endpoint all cause mortality
- Alternative arterial access possible

Enrollment expected to be completed in May 2013

CoreValve US Pivotal Trial Design

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What is the risk of stroke with TAVI?

- **TAVI (inoperable)**
  - Early strokes (2/3)
    - 27% within 24 hours
    - 55% between days 1-5
    - 18% after the first week
  - TAVI (high risk)
    - Early strokes (2/3)
      - 58% in the first 2 days
      - 17% between days 2-5
      - 25% between 5-30 days
  - Both groups, late strokes represented 1/3 of events

Risk of Stroke in PARTNER trial

<table>
<thead>
<tr>
<th></th>
<th>TAVI Stroke (major stroke)</th>
<th>Control Stroke (major stroke)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoperable</td>
<td>TAVI</td>
<td>*Standard Tx</td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>6.7% (5%)</td>
<td>1.7% (1.1%)</td>
<td>p=0.03  (p=0.06)</td>
</tr>
<tr>
<td>1 year</td>
<td>10.6% (7.8%)</td>
<td>4.5% (3.9%)</td>
<td>p=0.04  (p=0.18)</td>
</tr>
<tr>
<td>High Risk</td>
<td>TAVI</td>
<td>*AVR</td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td>5.5% (3.8%)</td>
<td>2.4% (2.1%)</td>
<td>p=0.04  (p=0.20)</td>
</tr>
<tr>
<td>1 year</td>
<td>8.3% (5.1%)</td>
<td>4.9% (2.4%)</td>
<td>p=0.04  (p=0.07)</td>
</tr>
</tbody>
</table>

Timing of the Stroke after the Procedures in the PARTNER trial

- AVR
  - 63% of major strokes within first 2 days
  - 25% between 5-30 days
  - 12% later than 30 days

Risk Factors for Post-Procedure Stroke in the PARTNER trial

- Independent risk factors for early strokes
  - TAVI
  - Smaller aortic valve area
- Independent risk factors for late strokes
  - Hx of stroke 6-12 months prior to the procedure
  - Non-transfemoral candidate (higher burden of atherosclerosis and vasculopathy)
  - Higher NYHA functional class

*Miller et al, J Thorac Cardiovasc Surg 2012*
Transcatheter Aortic-Valve Implantation (TAVI)

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Steps to decrease stroke...

- Lower profile valve and support frame
- ASA + Plavix
- Cerebral protection devices
  - Trials underway

Conclusions

- TAVI improves survival in inoperable patients with AS
- TAVI is an alternative to AVR in high-risk patients with AS, with a different set of complications
- Awaiting results from PIVOTAL trial
- Hopefully, changes in the technology will further improve outcomes.
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Not to stop future use and developments of this procedure

Future challenges and questions

1. How and when will TAVI expand to lower risk surgical patients
2. TAVI durability
3. Impact of TAVI residual paravalvular leakage
4. Impact of smaller delivery devices on transfemoral vs transapical and transition to percutaneous procedure
5. Impact of TAVI stroke complications and need for accessory devices

Thank You